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(54) Title: NOVEL SALT FORM OF PANTOPRAZOLE

(57) Abstract

The invention relates to the dihydrate of the magnesium salt of pantoprazole.

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Novel salt form of pantoprazole

Subject of the invention

The present invention relates to a novel salt form of the active compound pantoprazole. The novel salt form can be employed in the pharmaceutical industry for the preparation of medicaments.

Prior art

Pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0005129, EP-A-0166287, EP-A-0174726 and EP-A-0268956, have, on account of their H^+/K^+ ATPase-inhibiting action, considerable importance in the therapy of diseases which are due to increased gastric acid secretion. Examples of commercially available active compounds from this group are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl}-1H-benzimidazole (INN: rabeprazole).

A common property of the abovementioned pyridin-2-ylmethylsulfinyl-1H-benzimidazoles is the acid sensitivity - which is in the end indispensable for their efficacy - of these active compounds, which is seen in their strong tendency to decompose in a neutral and, in particular, acidic environment, strongly colored decomposition products being formed.

In the past, there have been considerable efforts, despite the acid sensitivity of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, to obtain stable and storable oral administration forms which contain these pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. Such stable and storable oral administration forms (e.g. tablets or capsules) are now obtainable. The preparation of these oral administration forms, however, is comparatively complicated and also certain precautions must be taken with respect to the packaging, in order that the administration forms have an adequate storage stability even under extreme storage conditions (e.g. in the tropics at high temperature and high atmospheric humidity).

The International Patent Application WO97/41114 describes a specific process for the preparation of magnesium salts of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. Inter alia, the preparation of the magnesium salt of pantoprazole is also described by way of example. According to the analysis data indicated, the salt prepared is pantoprazole magnesium in anhydrous form.

Description of the invention

It has now been found that the dihydrate of the magnesium salt of pantoprazole has very surprising stability properties which make it appear to be particularly suitable for use in solid or oral administration forms. It exhibits very considerably improved stability properties both in comparison with pantoprazole itself and in comparison to pantoprazole sodium sesquihydrate (the active compound form on the market since 1994, European Patent 0 589 981), or in comparison to pantoprazole sodium monohydrate (the intermediate form used in the industrial preparation, European Patent 0 533 790).

Thus pantoprazole magnesium dihydrate is completely stable for 4 days at 90°C and exhibits almost no discoloration or decomposition, while pantoprazole sodium sesquihydrate and monohydrate turn brown-red in the same period with formation of considerable amounts of decomposition products.

The invention thus relates to the dihydrate of the magnesium salt of pantoprazole (pantoprazole magnesium dihydrate).

Pantoprazole magnesium dihydrate can be employed for the treatment and prevention of all the diseases which are considered to be treatable or avoidable by the use of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. In particular, pantoprazole magnesium dihydrate can be employed in the treatment of disorders of the stomach.

On account of its solubility properties, possibilities of application for pantoprazole magnesium dihydrate are conceivable for whose realization resort had to be made up to now to particular pharmaceutical preparations. Thus use of pantoprazole magnesium dihydrate is particularly suitable, inter alia, where the active compound is to be released and absorbed over a relatively long period (see, for example, European Patent Application 0 841 903). By means of a combination of the magnesium salt of pantoprazole with the sodium salt, a solution made to order for certain desired active compound blood level courses can be achieved.

The pantoprazole magnesium dihydrate is prepared in a manner known per se by reaction of pantoprazole or a readily soluble pantoprazole salt (e.g. pantoprazole sodium) with a magnesium salt in water or in mixtures of water with polar organic solvents (e.g. alcohols, preferably ethanol or isopropanol, or ketones, for example acetone or butanone).

Suitable magnesium salts which can be employed according to the process are, for example, magnesium chloride, bromide, fluoride, iodide, formate, acetate, propionate, sulfate, gluconate or carbonate. Alkoxides of magnesium (e.g. magnesium methoxide, ethoxide, (iso)propoxide, butoxide, hexoxide or phenoxide), or magnesium hydroxide can also be reacted with pantoprazole or pantoprazole sodium in aqueous medium.

Example

Magnesium bis[5-[difluoromethoxy]-2-[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazolide] dihydrate

3.85 kg (8.9 mol) of pantoprazole Na sesquihydrate [sodium [5-[difluoromethoxy]-2-[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazolide]sesquihydrate] are dissolved at 20-25°C in 38.5 l of purified water in a stirring vessel. A solution of 1.0 kg (4.90 mol) of magnesium dichloride hexahydrate in 8 l of purified water is added with stirring at 20-30°C in the course of 3 to 4 h. After stirring for a further 18 h, the precipitated solid is centrifuged, washed with 23 l of purified water, stirred at 20-30°C for 1 to 2 h in 35 l of purified water, centrifuged again and washed again with 30-50 l of purified water. The solid product is dried at 50°C in vacuo (30-50 mbar) until a residual water content of < 4.8% is achieved. The product is then ground.

The title compound is obtained as a white to beige powder, which is employed directly for further pharmaceutical processing.

Yield: 3.40 kg (90% of theory); water content: 4.5-4.6%; melting point: 194-196°C with decomposition.

CHN analysis	C	H	N	S
Theory	46.58	3.91	10.19	7.77
Found	46.33	3.89	10.04	7.83

Alternatively the title compound can be produced using mixtures of organic solvents with water. For this, pantoprazole Na sesquihydrate is dissolved in an organic solvent at 50-60°C. 0.5 mole equivalents of the magnesium salt (e. g. magnesium chloride hexahydrate), dissolved in water, are added drop by drop and the solution is allowed to cool with stirring. The precipitated solid is filtered off, washed with the corresponding organic solvent and is dried in vacuo at 50°C to constant weight. The title compound is obtained as a colourless powder. Examples for different solvents are given in the following table 1.

Table 1:

pantoprazole Na sesquihydrate	organic solvent	water	yield of title compound	melting point ° C	water content %
50 g	isopropanol 300 ml	300 ml	45,4 g	196 – 197	4,4 – 4,5
50 g	isopropanol 300 ml	120 ml	45,9 g	196 – 197	4,3

pantoprazole Na sesquihydrate	organic solvent	water	yield of title compound	melting point ° C	water content %
50 g	ethanol 300 ml	300 ml	45,8 g	197 – 198	4,6
50 g	aceton 300 ml	300 ml	45,6 g	195 - 196	4,6, - 4,7

Alternatively the title compound can be produced by reacting pantoprazole with a basic magnesium salt, such as magnesium methylate, for example in the following manner: 90 g of pantoprazole are dissolved in 700 ml of 2-propanol at 60-70°C. 13.4 g (0.5 moles) of solid magnesium methylate are added, the solution is allowed to cool with stirring and filtered. After addition of 36 ml of water the crystalline solid formed is filtered off, washed with water and dried in vacuo at 50°C to constant weight. The title compound of melting point 194-196°C (water content 4.8 %) is obtained as beige solid.

Patent Claims

1. Pantoprazole magnesium dihydrate.

2. A medicament comprising pantoprazole magnesium dihydrate together with customary auxiliaries.

3. Pantoprazole magnesium dihydrate for use in the treatment of disorders of the stomach or intestine.

4. A combination medicament comprising pantoprazole magnesium dihydrate and pantoprazole sodium sesquihydrate.

5. A combination medicament comprising pantoprazole magnesium dihydrate and pantoprazole sodium sesquihydrate in the weight ratio (based on pantoprazole) of 10% pantoprazole magnesium dihydrate and 90% pantoprazole sodium sesquihydrate to 90% pantoprazole magnesium dihydrate and 10% pantoprazole sodium sesquihydrate.

6. A combination medicament comprising pantoprazole magnesium dihydrate and pantoprazole sodium sesquihydrate in the weight ratio (based on pantoprazole) of 25% pantoprazole magnesium dihydrate and 75% pantoprazole sodium sesquihydrate to 75% pantoprazole magnesium dihydrate and 25% pantoprazole sodium sesquihydrate.

7. A combination medicament comprising pantoprazole magnesium dihydrate and pantoprazole sodium sesquihydrate in the weight ratio (based on pantoprazole) of 40% pantoprazole magnesium dihydrate and 60% pantoprazole sodium sesquihydrate to 60% pantoprazole magnesium dihydrate and 40% pantoprazole sodium sesquihydrate.

8. A combination medicament comprising pantoprazole magnesium dihydrate and pantoprazole sodium sesquihydrate in the weight ratio (based on pantoprazole) of 50% pantoprazole magnesium dihydrate and 50% pantoprazole sodium sesquihydrate.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 99/05928

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 41114 A (ASTRA AB) 6 November 1997 (1997-11-06) cited in the application claims; example 10	1-8
A	WO 95 01977 A (ASTRA AB) 19 January 1995 (1995-01-19) claims	1-8
A	WO 91 19710 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK) 26 December 1991 (1991-12-26) claims	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 589 981 B (BYK GULDEN LOMBERG CHEMISCHE FABRIK) 23 October 1996 (1996-10-23) cited in the application page 4, line 50 - line 55; claims	1-8
A	EP 0 166 287 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK-) 2 January 1986 (1986-01-02) cited in the application page 23	1-8

INTERNATIONAL SEARCH REPORT

.ormation on patent family members

Interr nal Application No
PCT/EP 99/05928

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9741114 A	06-11-1997	SE 508669 C	26-10-1998
		AU 2719397 A	19-11-1997
		CA 2251636 A	06-11-1997
		CN 1216989 A	19-05-1999
		CZ 9803398 A	17-03-1999
		EP 0897386 A	24-02-1999
		HR 970210 A	30-04-1998
		NO 984903 A	21-10-1998
		PL 329683 A	12-04-1999
		SE 9601598 A	27-10-1997
WO 9501977 A	19-01-1995	AU 679766 B	10-07-1997
		AU 7198194 A	06-02-1995
		BR 9406940 A	10-09-1996
		CA 2166794 C	04-03-1997
		CN 1126993 A	17-07-1996
		CZ 9600069 A	15-05-1996
		DE 707580 T	04-09-1997
		EP 0707580 A	24-04-1996
		ES 2100136 T	16-06-1997
		FI 960101 A	09-01-1996
		GR 97300015 T	31-05-1997
		HR 940385 A	28-02-1997
		HU 75314 A	28-05-1997
		JP 8512315 T	24-12-1996
		MX 9405217 A	31-01-1995
		NO 960068 A	05-01-1996
		NZ 268693 A	26-05-1997
		PL 312440 A	29-04-1996
		SG 52464 A	28-09-1998
		SK 2296 A	01-10-1996
		US 5900424 A	04-05-1999
		ZA 9404933 A	20-02-1995
WO 9119710 A	26-12-1991	DE 4018642 A	12-12-1991
		AT 158793 T	15-10-1997
		AU 7956291 A	07-01-1992
		DE 59108863 D	06-11-1997
		DK 533790 T	14-04-1998
		EP 0533790 A	31-03-1993
		ES 2109946 T	01-02-1998
		GR 3025737 T	31-03-1998
EP 0589981 B	06-04-1994	AT 144416 T	15-11-1996
		AU 683411 B	13-11-1997
		AU 1974692 A	12-01-1993
		BG 61796 B	30-06-1998
		BG 98286 A	15-08-1994
		CA 2109697 A	23-12-1992
		CN 1067809 A,B	13-01-1993
		CZ 9302764 A	13-07-1994
		DE 4219390 A	24-12-1992
		DE 59207438 D	28-11-1996
		DK 589981 T	17-03-1997
		WO 9222284 A	23-12-1992
		EP 0519365 A	23-12-1992
		EP 0589981 A	06-04-1994
		ES 2096080 T	01-03-1997

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0589981 B		FI 935677 A	16-12-1993
		GR 3022154 T	31-03-1997
		HK 1005851 A	29-01-1999
		HR 920162 A	31-08-1996
		IE 77640 B	31-12-1997
		IL 102096 A	18-06-1996
		JP 6508118 T	14-09-1994
		LV 11982 A	20-03-1998
		LV 11982 B	20-09-1998
		MX 9202961 A	01-02-1993
		NO 934648 A	16-12-1993
		NZ 243147 A	21-12-1995
		PL 169951 B	30-09-1996
		RU 2089180 C	10-09-1997
		SK 128793 A	08-06-1994
		ZW 9392 A	17-02-1993
EP 0166287 A	02-01-1986	AT 45737 T	15-09-1989
		AU 578703 B	03-11-1988
		AU 4364085 A	19-12-1985
		BG 61322 B	30-05-1997
		CA 1254215 A	16-05-1989
		CS 9103964 A	16-09-1992
		CY 1670 A	10-10-1993
		DK 170440 B	04-09-1995
		ES 544204 A	01-06-1987
		GR 851399 A	25-11-1985
		HK 86894 A	02-09-1994
		IE 58117 B	14-07-1993
		IL 75400 A	31-10-1988
		JP 1647615 C	13-03-1992
		JP 3013234 B	22-02-1991
		JP 61022079 A	30-01-1986
		LU 88700 A	29-04-1996
		LV 5776 A	20-12-1996
		NZ 212415 A	29-03-1989
		PH 21850 A	25-03-1988
		PH 23729 A	03-11-1989
		PT 80641 A,B	01-07-1985
		SG 80192 G	04-12-1992
		SK 278401 B	09-04-1997
		US 4758579 A	19-07-1988